REMARKS

A. Status of the Claims

Claims 24-40, 42, 44, 45, and 61 are pending in the application. In the Action, the Examiner held that claims 41 and 43 are withdrawn from consideration, as drawn to non-elected species.

Claims 24-45 and 61 have been amended in the Amendment submitted herewith. No new matter has been added by these amendments.

Claims 24-40, 42, 44, 45, and 61 stand rejected by the Action.

Therefore, claims 24-45, and 61 are pending, of which claims 41 and 43 have been held withdrawn by the Examiner in the present Action as being drawn to a non-elected species. Reentry of these claims in view of the allowability of the other claims is requested below.

B. Claim 26 Is Not Indefinite

The Action rejects claim 26 under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Applicant respectfully traverses this rejection.

The Action argues that "the term 'equal marker' is vague and indefinite" (Action, p. 3, part G). Applicant respectfully disagrees with the Action's objection because the meaning of "equal" was plain in the context of the claim. Nonetheless, in the interest of advancing this claim, Applicant has altered the wording without altering the meaning of claim 26. The present claim is for "[t]he arrangement of claim 24, wherein said marker molecules are the same fluorescent dye." This is supported in the Application Publication (U.S. Patent Application Publication No. US 2002/0030811 A1, March 14, 2002, hereinafter "Application") at page 4, paragraphs 0049 and 0050, where it is taught that, in the context of the invention, one can use the claimed arrangement "with *a* dye" (emphasis supplied) or "with different fluorescence dyes."

In view of the above, the rejection under 35 U.S.C. § 112, second paragraph, is overcome.

C. Claims 24, 26-40, 42, 44, 45, and 61 Are Not Indefinite

The Action rejects claims 24, 26-40, 42, 45, and 61 under 35 U.S.C. § 112, second paragraph as being indefinite and/or unclear. The Action maintains that "the term 'large-area' [in claim 24] is a relative term, which renders the claim indefinite and/or unclear" (p. 9, section BB). Applicant respectfully traverses this rejection.

To overcome this rejection, Applicant submits the declaration of Max Sonnleitner, Ph.D. under 37 C.F.R. § 1.132 (hereinafter the "Sonnleitner Declaration") (attached hereto as Appendix A). Dr. Sonnleitner is Head of the "Ultra-sensitive Fluorescence Microscopy/Device Development" group at the Center for Biomedical Nanotechnology of the Upper Austrian Research GmbH in Linz, Austria. He has over 7 years of research experience and has published numerous peer-reviewed publications in the field of fluorescence microscopy. He is an expert in the area of fluorescence microscopy, including single molecule detection and single dye tracing (Sonnleitner Declaration, paragraph 1).

According to the Sonnleitner Declaration, to one of ordinary skill in the art, the term "large-area fluorescent excitation" as used in claim 24 is synonymous with the term "wide-field" microscopy:

> Those of skill in the field of fluorescence microscopy understand that "wide-field microscopy" is a technique employed in single dye tracing, wherein a large area of between 100 μm^2 (the size of a small single biological cell) to 10,000 μm^2 is evenly and simultaneously illuminated while its image is recorded. The term "large-area fluorescent excitation" as used in the specification and claims has the same meaning to one of skill in the field of fluorescence microscopy as the term "wide-field illumination."

(Sonnleitner Declaration, paragraph 3). There is nothing indefinite or unclear about Applicant's use of the term "large-area fluorescent microscopy." *In re Castaing*, 429 F.2d 461, 463 (CCPA 1970) ("An applicant is ordinarily allowed to be his own lexicographer, so long as his meaning is clear, as it is here."). Therefore, the definitional and practical distinctions detailed in the Peter J. Shaw reference cited in the 7/26/04 Response apply equally to "wide-field microscopy" and the synonymous term "large-area fluorescent excitation." The relevant excerpt is reproduced below, with "large-area fluorescent excitation" substituted for "wide-field microscopy:"

> Laser-scanning confocal and [large-area fluorescent excitation] differ markedly in the way the fluorochrome molecules in the specimen are excited. In [large-area fluorescent excitation], each plane of the specimen is evenly illuminated while its image is recorded. In a scanning confocal microscope, the illuminating beam rapidly traverses the specimen, giving very high light intensity at the center of the focal spot and rapidly decreasing intensity over a broad region above and below this spot. The instantaneous light distribution is given approximately by the form of the WF-PSF (although the focused laser beam has a somewhat different detailed distribution). The very high light intensity can easily saturate the fluorochromes at the center of the focal spot, and the need to avoid this, in turn, limits the excitation intensity that can be used effectively. When the laser light intensity is reduced enough to avoid saturation, the amount of emitted light recorded is very small (10-20 photons/pixel) for most fluorescent biological specimens, and it is necessary to sum the light from many scans. Thus, each part of the specimen is illuminated by a succession of high-intensity pulses of light.

Peter J. Shaw; in *Handbook of Biological Confocal Microscopy*, 1995 (Appendix B, 379). As the above reference makes clear, there are substantive differences as well as important practical considerations in deciding which form of microscopy to employ. Thus, far from being "indefinite and/or unclear" as the Action argues, the term "large-area" actually defines the basic category of fluorescence microscopy upon which this invention is based.

The Action rejects the entire claim set of independent claim 24 and its dependent claims, 26-40, 42, 45, and 61, with a single argument directed at claim 24. Therefore, Applicant has responded to the rejection of claim 24 specifically, and this response applies to the same set of

claims, 24, 26-40, 42, 45, and 61. *See In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997) ("In the absence of a separate argument with respect to the dependent claims, those claims stand or fall with the representative independent claim.").

In view of the above, the rejections to independent claim 24 and its dependent claims, claims 26-40, 42, 45, and 61, as being indefinite and/or unclear are overcome. Applicant respectfully requests that these claims be allowed.

D. Claim 25 is not directed to non-statutory subject matter nor is it unclear

The Action enters a new rejection to claim 25 under 35 U.S.C. § 101 as well as 35 U.S.C. § 112, second paragraph as being unclear and indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Action maintains that claim 25 is for a product, the biological cells in the apparatus described in claim 24. Applicant respectfully traverses this rejection.

Applicant respectfully disagrees with the Action's interpretation that claim 25 claims biological cells. Present claim 25 is for "[t]he arrangement of claim 24, further defined as comprising biological cells in the sample holder." Claim 24 is for "[a]n arrangement adapted to visualize molecules." The embodiment claimed in claim 25 is specifically one in which the claimed arrangement further comprises the additional limitation of biological cells in the sample holder. Applicant is claiming this apparatus, *and is not attempting to claim the biological cells by themselves*. Claim 25 thus is neither indefinite nor directed to non-statutory subject matter and these rejections are overcome.

E. Claim 24 and Its Dependent Claims (25-28, 30-35, 37 and 61) are Patentable Over Sharonov, Sanchez, and Lewis

The Action rejects claims 24-28, 30-34, and 61 under 35 U.S.C. § 102(b) as being anticipated by Sharonov, *et al.* (Sharonov, S., *et al.* "Confocal spectral imaging analysis in

studies of the spatial distribution of antitumor drugs within living cancer cells." *Analytica Chemica Acta* 290 (1994) 40-47, hereinafter "Sharonov") and enters a new rejection under the same section against claims 24, 26, 27, 30, 32, 34, 35, 37, and 61 as being anticipated by Sanchez, *et al.* (Sanchez, E., *et al.* "Room-temperature fluorescence imaging and spectroscopy of single molecules by two-photon excitation." *The Journal of Physical Chemistry A* 101(38) (1997) 7019-7023, hereinafter "Sanchez"). The Action also enters a new rejection under 35 U.S.C. § 103(a) against claims 24, 26, 27, 29, 30, 32, 34, 35, 37, 44, and 61 as being unpatentable over Sanchez and Lewis, *et al.* (U.S. Patent No. 5,705,878, hereinafter "Lewis"). Applicant respectfully traverses these rejections.

It is axiomatic that if a reference does not have "each and every element as set forth in the claim," that claim is not anticipated by the reference. MPEP § 2131 (citing *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987)); *see also* MPEP § 2131.02 (citing *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989) ("The identical invention must be shown in as complete detail as is contained in the patent claim")). Present claim 24 is directed to:

> An arrangement adapted to visualize molecules, comprising:
>
> > at least one source of light adapted for large-area fluorescent excitation, via single or multiple photon absorption, of marker molecules in said sample during use;
> >
> > a sample holder;
> >
> > a detection and analysis system comprising a charged coupled device (CCD) camera, wherein at least one of the sample holder and the detection and analysis system is movable laterally, relative to the other during use; and
> >
> > a control unit adapted to coordinate and synchronize illumination times and lateral movement between said sample holder and said detection and analysis system during use;

> wherein the arrangement is adapted to visualize movements of molecules, interactions between molecules, and molecular processes in a sample during use, by using a single dye tracing (SDT) method.

Contrary to what the Action asserts, neither Sharonov nor Sanchez anticipate every element of claim 24.

1. Sharonov and Sanchez Do Not Teach An Apparatus Adapted to Visualize Movements of Molecules, Nor Do They Teach an Adaptation of the Single Dye Tracing Method

A key aspect of the present invention is the ability to "visualize movements of molecules, interactions between molecules, and molecular processes in a sample" as specified in claim 24. At the time of the application, the only known microscopy technique that could be used to visualize the movements of molecules was single dye tracing (Application, p. 1, paragraph 0009). Nowhere do either the Sharonov or Sanchez references teach an apparatus "adapted to visualize movements of molecules ... by using a single dye tracing (SDT) method." In spite of this, the Action rejects claim 24 on the grounds that the limitations of visualizing moving molecules and using a single dye tracing method in claim 24 have "not been given patentable weight" because the recitations occurred in the preamble (Reason 2, p. 9). Applicant respectfully disagrees with the proposition that limitations in the preamble cannot be given patentable weight. *See In re Paulsen*, 30 F.3d 1475, 1479 (Fed. Cir. 1994) ("Terms appearing in a preamble may be deemed limitations of a claim when they give meaning to the claim and properly define the invention.").

Nonetheless, in the interest of advancing this claim, the limiting phrases "movements of molecules, interactions between molecules molecular processes in a sample during use" and "by using a single dye tracing (SDT) method" are found in the body of present claim 24 rather than the preamble. Accordingly, the ability to "visualize movements of molecules, interactions

between molecules, and molecular process in a sample during use" as well as employment of "a single dye tracing method" are limitations on claim 24. Neither Sharonov nor Sanchez "visualize movements of molecules" nor does either Sharonov or Sanchez employ the SDT method. Therefore, neither Sharonov nor Sanchez anticipate every element of claim 24.

2. Large-Area Fluorescent Excitation Is Not an Inherent Property of a Laser

a. Sharonov and Sanchez Do Not Illuminate a Region of At Least 100 μm^2 In the Same Manner As Applicant

Sharonov and Sanchez both teach the use of a laser in confocal microscopy, not large-area fluorescent excitation (Sharonov, p. 41; Sanchez, p. 7019). Contrary to the suggestions of the Action, a laser used in confocal microscopy is not inherently adapted to large-area fluorescent excitation of an area of at least 100 μm^2 (Action bottom of p. 5, middle of p. 15). Sharonov teaches *scanning* a 20×20 μm region *over the course of 10 minutes*. Sharonov at 42 (emphasis added). Similarly, the Action contends that Sanchez discloses the excitation of a 10×10 μm region in the same manner as the Applicant, but Sanchez actually discloses "a line scan rate of 1 Hz," again demonstrating that Sanchez is scanning across the sample, not illuminating the entire sample simultaneously (Sanchez, p. 7020, 7022).

b. It Is Impossible To Illuminate a Region of At Least 100 μm^2 Using the Methods Taught By Sharonov and Sanchez

According to the Sonnleitner Declaration, the illumination area of a laser in confocal microscopy, as specified by Sharonov and Sanchez, is much smaller than the Action maintains:

> ... those of skill in the field of fluorescence microscopy understand that, in "confocal microscopy," a laser is focused on a focal spot on the sample. The diameter of this spot is $\frac{1.2\times\lambda}{NA}$, where λ is the wavelength of the laser and NA is the numerical aperture of the objective. The wavelengths (λ) of lasers commonly used in fluorescence microscopy range from 0.4 to 0.7 μm. The numerical apertures (NA) of commonly used objectives are 1 to 1.4. Thus, the diameter of

> the focal spot of the laser ranges from 0.340 μm to 0.840 μm, or well below 1 micrometer.

(Sonnleitner Declaration, paragraph 4). The Sonnleitner Declaration continues that, "[i]n view of the above, it is impossible to evenly illuminate an area of 100 μm^2 using 'confocal microscopy.'" (paragraph 5). Thus, while both large-area fluorescent excitation and confocal microscopy use a laser, the specific method in which the laser is employed, as well as the effect of the laser, are very different in the two methods. Thus, large-area fluorescent excitation is not, as the Action maintains, an inherent property of a laser.

3. *Sharonov and Sanchez Teach Nothing About Single Dye Tracing or Large-Area Fluorescent Microscopy*

The Sonnleitner Declaration also sets forth that Sharonov and Sanchez are both irrelevant to claim 24 because they teach a different type of microscopy:

> The references of Sharonov, *et al.* and Sanchez, *et al.*, which I have read, are related to "confocal microscopy" as that term is understood to those skilled in the field of fluorescence microscopy. These references teach nothing to one of skill in the field of fluorescence microscopy about "large-area fluorescent excitation" or "single dye tracing," as described in the above-referenced application and claim.

(Sonnleitner Declaration, paragraph 5) (citations omitted). If neither Sharonov nor Sanchez teach either large-area fluorescent excitation or single dye tracing, then they cannot anticipate every element of claim 24. Therefore, contrary to what the Action maintains, neither Sharonov nor Sanchez can anticipate claim 24 under 35 U.S.C. § 102(b).

Finally, as the Action notes on p. 19, section 13, the sole justification for arguing that claim 24 is obvious under Sanchez is that it is anticipated by Sanchez: "Sanchez et al. anticipate[] and, as a result, render[] obvious...." It must thus follow that if claim 24 is not anticipated by Sanchez, then it cannot be obvious under Sanchez, either. MPEP § 2143.03 ("To

establish *prima facie* obviousness of a claimed invention, all other claim limitations must be taught or suggested by the prior art.") (citing *In re Royko*, 490 F.2d 981 (CCPA 1974)).

4. Lewis Teaches Nothing About Single Dye Tracing or Large-Area Fluorescent Microscopy

The Action rejects dependent claims 29 and 44 under 35 U.S.C. § 103(a) as being unpatentable over Sanchez and Lewis. Applicant respectfully traverses this rejection.

As previously noted, *infra*, Sanchez teaches nothing about single dye tracing or large-area fluorescent microscopy, the methods employed in the present invention, because Sanchez teaches only confocal microscopy. As the Action repeatedly acknowledges on pages 20 and 21, the limitations taught by Lewis also apply specifically to confocal, not large-area fluorescent, microscopy. Action, p. 20 ("Lewis et al. explicitly states that their 'flat design' is 'particularly well suited for ... *confocal* optical microscopy' which would encompass the *confocal* microscopy apparatus disclosed by Sanchez et al.") (quoting Lewis at column 1, lines 11-14) (emphasis supplied); *Id.* ("... Lewis et al. explicitly state that their invention is 'ideally suited for stage scanning *confocal* optical microscopy. Its inherent axial positioning capability provides a mechanism for optically slicing a sample in the z direction while *scanning it through the confocal spot.*'") (quoting Lewis at column 2, lines 40-45) (emphasis supplied).

If neither Sanchez nor Lewis teaches large-area fluorescent excitation and single dye tracing, then they cannot anticipate every element of claims 29 and 44, which are dependent on claim 24. Therefore, contrary to what the Action maintains, Sanchez in combination with Lewis cannot anticipate claims 29 and 44 under 35 U.S.C. § 102(b).

For at least these reasons, independent claim 24 and its dependent claims, claims 25-35, 37, 44, and 61, are patentable over Sharonov, Sanchez, and Lewis. *See Hartness International, Inc. v. Simplimatic Engineering Co.*, 819 F.2d 1100, 1108 (Fed. Cir. 1987) (holding that

dependent claim was nonobvious and novel because it contained all the limitations of a valid independent claim, plus a further limitation); *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1576 n. 36 (Fed. Cir. 1987). Applicant respectfully requests that these claims be allowed.

F. Claims 24-40, 42, 44, 45, and 61 are patentable over Schmidt, Lewis, Albertine, and Al-Ghoul

The Action enters a new rejection against claims 24-40, 42, 44, 45, and 61 under 35 U.S.C. § 103(a) as being unpatentable over Schmidt, *et al.* (Schmidt, Th., *et al.* "Imaging of single molecule diffusion." 93 *Proc. Natl. Acad. Sci. USA* (1996) 2926–2929, hereinafter "Schmidt") and Lewis as evidenced by Schmidt, *et al.*, (Schmidt, Th., *et al.* "Microscopy for Recognition of Individual Molecules." 29(1) *Laser und Optoelektronik* (1997) 56-62), Albertine, *et al.* (Albertine, K., *et al.* "Morphological analysis of the activation of adherent neutrophils in vitro." 20(4) *Tissue Cell* (1998) 519-530, hereinafter "Albertine"), and Al-Ghoul, *et al.* (Al-Ghoul, K., *et al.* "Light Microscopic Variation of Fiber Cell Size, Shape and Ordering in the Equatorial Plane of Bovine and Human Lenses." 3 *Molecular Vision* (1997) 2, hereinafter "Al-Ghoul").

The Action maintains that Schmidt teaches a method for imaging single molecule diffusion, which is said to read on claim 24. Applicant respectfully traverses this rejection.

It is axiomatic that, "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." MPEP § 2143.03 (citing *In re Royka*, 490 F.2d 981 (CCPA 1974); *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970)). Thus, if a claim limitation exists that it *not* taught or suggested by the prior art, obviousness has not been established. Present claim 24 is directed to:

> An arrangement adapted to visualize molecules, comprising:
>
> at least one source of light adapted for large-area fluorescent excitation, via single or multiple photon absorption, of marker molecules in said sample during use;

a sample holder;

a detection and analysis system comprising a charged coupled device (CCD) camera, wherein at least one of the sample holder and the detection and analysis system is movable laterally, relative to the other during use; and

a control unit adapted to coordinate and synchronize illumination times and lateral movement between said sample holder and said detection and analysis system during use;

wherein the arrangement is adapted to visualize movements of molecules, interactions between molecules, and molecular processes in a sample during use, by using a single dye tracing (SDT) method.

A key advantage of the present invention is the ability to "visualize movements of molecules, interactions between molecules, and molecular processes in a sample" (claim 24) wherein the sample may comprise a biological cell or cells (claim 25). Unlike the present invention, Schmidt does not teach the visualization of movements of molecules, interactions between molecules, and molecular processes within a three-dimensional biological cell or cells; it only discloses artificial flat-surface lipids (Schmidt at bottom of first column, p. 2926; top of second column, p. 2926).

Further, nowhere does Schmidt teach "a control unit adapted to coordinate and synchronize ... lateral movement between said sample holder and said detection system," nor does Schmidt teach "at least one of the sample holder and the detection and analysis system is movable laterally, relative to the other during use." These differences were previously explained in the January 23 Response on pages 14 and 15, and subsequent Actions on April 21, 2004 and February 23, 2005 have never addressed these important differences. In light of this silence, it is puzzling that the present Action argues that Schmidt renders the present invention obvious.

Neither Schmidt nor any of the secondary references teaches or suggests each element of claim 24. The Action thus does not meet the burden of establishing a *prima facie* case of

obviousness, and therefore claim 24 is not obvious and must be patentable over Schmidt in combination with Lewis, Albertine, and Al-Ghoul.

For at least these reasons, independent claim 24 and its dependent claims, 25-40, 42, 44, 45, and 61 are patentable over Schmidt and the secondary references. MPEP § 2143.03 ("If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious.") (citing *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988)). Applicant respectfully requests that these claims be allowed.

G. Entry of Non-elected Species Is Requested

In view of the forgoing arguments, all the presented claims are in condition of allowance. Thus, all species contained in the dependent claims withdrawn by the examiner (claims 41 and 43) should be reentered into the case and allowed. Applicant respectfully requests that all such dependent claims be considered and allowed.

H. Conclusion

Applicant respectfully submits that claims 24-45 and 61 are in condition for allowance.

REQUEST FOR EXTENSION OF TIME

Pursuant to 37 C.F.R. § 1.136(a), Applicants petition for an extension of time of one month to and including June 23, 2005, in which to respond to the Office Action dated February 23, 2005.

Pursuant to 37 C.F.R. § 1.17, a check in the amount of $60.00 is enclosed, which is the process fee for a one-month extension of time for a small entity status. If the check is inadvertently omitted, or should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an overpayment be included, the Commissioner is authorized to deduct or credit the appropriate fees from or to Fulbright & Jaworski Deposit Account No. 50-1212/SONN:010US.

The Examiner is invited to contact the undersigned Attorney at (512) 536-3035 with any questions, comments, or suggestions relating to this patent application.

Respectfully submitted,

Mark B. Wilson by.
Gilbert A. Greene
Reg. No. 48,366

Mark B. Wilson
Reg. No. 37,259
Attorney for Applicant

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 536-3035

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